Appendices - Advancing Male Contraception

Capstone Project

Contents

Appendix A - Thesis Statement

YCT-529 represents a groundbreaking advancement in male contraception, utilizing a non-hormonal mechanism that specifically targets and inhibits retinoic acid receptor-α (RAR-α) to disrupt spermatogenesis. This review argues that, unlike traditional female-centric contraceptive methods, YCT-529 offers a novel approach that avoids the hormonal modulation often associated with significant side effects. By employing a molecular design featuring a chromene core, pyrrole linker, and benzoic acid moiety, YCT-529 achieves high selectivity and binding affinity for RAR-α, resulting in a 99% reduction in sperm production in preclinical murine models with full reversibility within 4 weeks [40]. Pharmacokinetic analysis revealed a half-life of 11 hours and peak plasma levels of 2.1 µM, ensuring sustained systemic exposure and targeted testicular action [50]. Non-human primate studies demonstrated complete suppression of sperm production with oral doses of 10–20 mg/kg/day, without systemic toxicity [50]. This thesis contends that YCT-529 signals a paradigm shift in contraceptive medicine, with transformative implications for future contraceptive research, public health policy, and the equitable distribution of reproductive responsibility.

Appendix B - Medium Article

For a more intuitive explanation of the science behind YCT-529, including its mechanism of action and role in retinoic acid signaling, please refer to the Medium article: Unlocking Male Contraception: The Science Behind YCT-529 and Retinoic Acid Signaling.

Appendix C - Extended Discussion on Contraception

Contraception

Contraception, fundamentally, represents a method or device designed to prevent pregnancy as a consequence of sexual intercourse. Its core principle hinges on controlling fertility and enabling individuals to decide if and when to have children, a matter deeply intertwined with personal autonomy and bodily integrity [4]. Contraceptive methods span from barrier options, hormonal interventions, to surgical procedures, each with varying degrees of effectiveness and modes of action. Their utilization extends across diverse populations, affecting both men and women, with profound ethical implications regarding accessibility, informed consent, and the right to reproductive freedom [4].

Orally administered contraceptives, usually in pill form, typically contain hormones or agents that obstruct the natural reproductive flow. Other contraceptive methods include intrauterine devices (IUDs), subdermal implants, vaginal rings, patches, and injectables,

each delivering hormones or creating physical barriers differently. These variations raise ethical questions around bodily autonomy, as they interact uniquely with the body's hormonal cycle, potentially altering it in ways that can have significant side effects [4]. The ethical considerations here involve the balance between efficacy and safety, as individuals must weigh the benefits of preventing unintended pregnancies against the potential health risks these methods pose.

Hormonal contraceptives, such as Levonorgestrel or Ulipristal Acetate, release synthetic hormones like progestin and estrogen to modify reproductive functions, either preventing ovulation in women or inhibiting sperm production in men [23]. Non-hormonal methods, by contrast, create physical or chemical barriers without altering hormonal balance. These include copper IUDs and condoms, which present fewer systemic side effects, thereby offering ethically preferable options for those seeking to avoid the complex ethical implications associated with hormonal manipulation. These methods highlight the ethical imperative to provide diverse contraceptive options that respect individual preferences and medical conditions, ensuring that choices in contraception are aligned with personal values and health needs.

The push towards non-hormonal male contraceptive research emerges from ethical concerns about the adverse effects of hormonal contraceptives. Altering the natural hormonal balance in men can lead to side effects like decreased libido, mood swings, weight gain, and long-term fertility and health impacts [38]. These side effects are not merely physical inconveniences but have significant psychological implications. For instance, decreased libido and mood swings can impact a man's self-esteem, emotional well-being, and relationships, potentially leading to anxiety, depression, or relational discord. These potential harms raise ethical questions about the fairness and responsibility of subjecting individuals to treatments that can cause psychological distress when safer alternatives could be developed. Ensuring that new contraceptive methods prioritize patient safety and minimize both physical and psychological adverse effects is crucial not only for individual health but also for building trust in medical innovations. This strategic focus aims to enhance patient compliance, reduce long-term health complications, and alleviate healthcare system burdens, ultimately serving the broader public interest in reproductive health.

The pursuit of safer male contraceptives is integral to promoting shared responsibility in family planning, challenging the longstanding ethical imbalance that has placed the burden predominantly on women. Increased male participation in contraceptive use is associated with positive social and health-related outcomes, fostering improved communication and more equitable gender attitudes among partners [38]. From a psychological standpoint, shared responsibility in contraceptive use can lead to improved relationship satisfaction and a sense of partnership, as couples navigate family planning decisions together. To shape this behavior effectively, various incentives and choice architecture

strategies can be employed.

First, **incentives** such as highlighting the relational benefits of shared contraceptive responsibility can motivate men to take a more active role. From a psychological perspective, men may be more inclined to engage in behaviors that are framed as enhancing relationship dynamics. By emphasizing how male contraceptives can enhance mutual trust, communication, and equality in relationships, men may perceive a higher utility in participating. This framing leverages psychological theories of social reinforcement, where positive relational outcomes serve as reinforcement for behavior change. Moreover, promoting the fact that non-hormonal male contraceptives, like YCT-529, come with fewer side effects compared to female hormonal contraceptives acts as an incentive, potentially increasing the willingness to adopt these options. This incentive also appeals to the psychological drive to avoid adverse experiences, such as the discomfort associated with hormonal side effects, thus enhancing the appeal of non-hormonal alternatives.

Second, employing **choice architecture** can further shape behavior by making male contraceptive options more visible and accessible. For example, healthcare providers can introduce these options during routine medical consultations, ensuring they are presented alongside female contraceptive methods. This strategy draws on principles of behavioral psychology, where individuals are more likely to choose an option that is easily accessible and presented as a normative choice. By including male contraceptives in discussions about family planning, men are 'nudged' towards considering these options as part of a standard reproductive health strategy, even if they were not actively seeking contraceptive solutions. This nudge operates on the psychological premise that individuals often rely on heuristic decision-making, where the ease of access and presentation of an option can significantly influence behavior.

This combination of incentives and choice architecture creates a **positive feedback loop**: as more men become aware of the benefits and accessibility of male contraceptives, their adoption rates increase. This rising participation further normalizes the use of male contraceptives, leading to increased demand for innovative, non-hormonal options. In turn, this demand drives further research and development in male contraception, expanding available options and reinforcing the shift toward shared reproductive responsibility [37]. This feedback loop not only supports gender equity but also encourages a more balanced partnership, enhancing overall outcomes for both partners and promoting a societal model where contraceptive responsibility is equally shared. Psychologically, this normalization process also reduces stigma and fosters a supportive environment for men to engage in contraceptive use, reducing anxiety and social pressure associated with deviating from traditional gender norms.

Historically, the focus on female contraceptives often placed women at significant health risks due to inadequate research on long-term effects and hormonal impacts. Early contraceptive pills, for example, contained high hormone doses linked to serious side ef-

fects like blood clots and heightened cancer risks [23]. This legacy reflects an ethical oversight in medical research and development, which failed to fully consider the long-term health consequences for women. This imbalance necessitates a paradigm shift toward safer, more equitable developments in contraceptive technology, including a greater emphasis on male contraceptive options. Addressing this disparity is not just a medical priority but an ethical obligation to ensure fairness in reproductive health responsibilities.

From a sociological perspective, the ethical development of male contraceptives that minimize side effects addresses crucial aspects of fairness and equality within gender dynamics and healthcare. By redistributing contraceptive responsibility more evenly, this approach seeks to alleviate the disproportionate health risks historically borne by women, promoting a more equitable societal model where both partners are equally invested in family planning. This model supports gender equity in relationships, reduces psychological stress, and enhances autonomy across genders, aligning with ethical principles of justice and equality.

From a psychological perspective, the availability of non-hormonal oral male contraceptives significantly influences the mental and emotional aspects of family planning. For men, having reliable, reversible contraceptive options enhances their mental preparedness for parenthood, allowing them to actively decide when they are ready to father children. This autonomy can reduce anxiety and increase life satisfaction by aligning childbearing decisions with personal and professional goals, addressing the ethical value of individual agency in reproductive choices. Furthermore, the ability to take proactive steps in family planning can foster a sense of control and empowerment, which is associated with positive mental health outcomes.

Therefore, the development of non-hormonal male contraceptives, which do not alter the body's hormone levels and minimize the risk of adverse side effects, is not merely a medical advancement but an ethical imperative. It represents a crucial step towards advancing social justice in reproductive health by offering safer, more equitable options for family planning [38]. From a psychological viewpoint, this shift not only alleviates the individual and relational stressors associated with family planning but also contributes to a more balanced and inclusive approach to reproductive health.

Appendix D - Extended Discussion on Condoms and Vasectomies

Condoms

Condoms, particularly male condoms, have been a cornerstone in both contraceptive practices and sexually transmitted infection (STI) prevention for centuries. Their evolution from primitive materials like oiled silk paper and animal intestine to the advanced latex and polyurethane versions used today reflects significant technological and material advancements. The early documentation of condoms dates back to ancient civilizations, with significant developments noted by Gabriello Fallopio in the 16th century, who described a linen sheath used for syphilis prevention. This was further revolutionized in the 19th century by Charles Goodyear's vulcanization process, paving the way for the first rubber condoms [33]. Today, male condoms are primarily made from latex, known for its strength and elasticity, providing a reliable barrier against the exchange of bodily fluids and thus, reducing the transmission risk of a wide range of STIs, including HIV, gonorrhea, and chlamydia.

Functionally, male condoms act as a barrier device that is rolled onto an erect penis before intercourse to prevent semen from entering the partner's body, thereby also preventing pregnancy. The efficacy of condoms is highly dependent on correct and consistent use. With perfect use, male condoms are 98% effective at preventing pregnancy, but with typical use, their effectiveness drops to about 85% due to errors in application or inconsistent use during every sexual encounter. Moreover, while condoms are effective in reducing the transmission of most STIs, their protective efficacy varies across different infections. For instance, they offer more than 90% protection against HIV and hepatitis B but are less effective against viruses like human papillomavirus (HPV) and herpes simplex virus (HSV), where transmission may occur through skin-to-skin contact with exposed areas not covered by the condom [33].

Advantages, Limitations, and Future Directions in Condom Use

The primary advantages of male condoms lie in their accessibility, ease of use, and provision of protection against both STIs and pregnancy. They are a non-invasive, non-hormonal method of contraception that can be used on demand, making them particularly valuable in diverse sexual health contexts. From a psychological perspective, the ability to use condoms on demand provides individuals and couples with immediate control over their reproductive choices, which can contribute to a sense of autonomy and empowerment during sexual activities. Additionally, they are among the most economical forms of contraception available on the market, making them an appealing option for individuals across different socioeconomic backgrounds, thus potentially reducing the

cognitive burden associated with long-term family planning.

However, the usage of condoms also comes with several challenges. Several studies show that the incorrect use, such as late application or early removal, can significantly diminish their effectiveness [57, 14]. From a behavioral standpoint, these issues can be attributed to a combination of lack of education, cognitive errors, and impulsive decision-making during sexual encounters. The need for correct and consistent use places a cognitive load on individuals, especially in high-arousal situations where decision-making can be compromised. Condom breakage or slippage during intercourse further complicates their reliability, which can lead to psychological stress and anxiety about potential pregnancy or STI exposure. Furthermore, latex allergies can pose serious health risks for some users, necessitating alternatives like polyurethane or polyisoprene condoms, which are generally more expensive. This health concern can affect the psychological willingness to use condoms, as individuals may associate condom use with discomfort or health risks.

In a comprehensive review titled *"Acceptability of male condom: An Indian scenario,"* Donta et al. (2014) explored the utilization patterns of condoms within the Indian demographic context. They observed that a predominant concern about the side effects associated with alternative contraceptive methods significantly influences both males and females toward choosing condoms as a safer option. This behavior can be understood through the lens of the health belief model, which posits that individuals' willingness to engage in health-promoting behaviors, such as condom use, is influenced by perceived susceptibility to health risks and the perceived benefits of taking preventive action. The study highlighted that a considerable proportion of individuals—irrespective of gender—opt to discontinue the use of contraceptives, particularly hormonal types, within the first year of usage due to adverse side effects [15]. This decision-making process is shaped by the interplay of psychological factors such as fear of adverse effects, personal beliefs about contraception, and social influences. Despite these concerns, the actual usage rates of condoms remain relatively low among the sexually active population. This underutilization is primarily attributed to societal stigmas and entrenched cultural norms that deter open discussions and acceptance of condom use, thereby limiting its widespread adoption despite its recognized safety and efficacy. From a social psychology perspective, the societal stigma around condom use can lead to internalized norms that affect individual behavior, causing reluctance to use condoms even when individuals recognize their importance for sexual health.

Future developments in condom technology are focusing on enhancing the user experience and increasing protective efficacy. Innovations such as graphene-infused condoms aim to improve durability and heat transfer, potentially increasing pleasure and acceptance. This addresses the psychological barrier of reduced sensation, a common complaint that often leads to reluctance in condom use. By enhancing the sensory experience, these innovations may improve the psychological acceptability of condom use, aligning with

the theory of planned behavior, which suggests that increasing positive attitudes toward a behavior can enhance the intention and likelihood of performing that behavior. Nano-lubricated condoms are being designed to provide a longer-lasting and less irritating lubrication, addressing one of the common drawbacks of traditional latex condoms. This can help alleviate concerns about discomfort, thus reducing the psychological resistance to consistent condom use. Moreover, the development of condoms with integrated microbicides that offer additional protection against STIs represents a promising frontier in the enhancement of condom functionality [33]. This added layer of protection may appeal to individuals' health consciousness, further motivating the use of condoms.

In conclusion, while male condoms continue to play a pivotal role in sexual health and reproductive strategies globally, ongoing research and development are critical in addressing their limitations and improving their protective capabilities. The enhancement of condom technology not only aims at increasing their physical reliability but also at broadening their acceptance and consistent use across populations, thereby contributing significantly to global public health outcomes. By addressing the psychological barriers to condom use, such as discomfort, stigma, and reduced sensation, these innovations have the potential to promote safer sexual practices and foster a more health-conscious society. Through this multidimensional approach, condom technology can evolve to meet both the physical and psychological needs of individuals, supporting more effective family planning and sexual health strategies.

Vasectomies

Vasectomy stands as a definitive male sterilization technique that involves the transection and sealing of the vas deferens to prevent sperm from entering the ejaculate, thus offering a permanent method of contraception. The procedure's inception can be traced back to the early 20th century, gaining widespread acceptance due to its simplicity and high efficacy rate [27]. Vasectomy typically boasts a success rate of 99.7%, coupled with a low complication rate of 1% to 2%, making it a favored option among permanent contraceptive methods [52].

The procedure operates on a straightforward principle: severing the vas deferens, the tubes that carry sperm from the testes to the urethra. This is typically achieved through one of several techniques, including the conventional approach involving a small incision or the no-scalpel method, which uses a puncture to access and obstruct the vas deferens, thus reducing tissue damage and potential complications. Once the vas deferens is cut, the ends are sealed, either by suturing, cauterizing, or applying clips, effectively preventing sperm from mixing with the semen produced by the seminal vesicles. Notably, a vasectomy does not affect the production of male hormones or the secretion of other fluids that constitute the semen, ensuring that sexual functions, including libido and

erectile function, remain unaltered.

Efficacy and Prospective Complications

The protective efficacy of vasectomy is notably high, with less than a 0.3% chance of pregnancy post-confirmation of sperm absence in the ejaculate through post-vasectomy semen analysis (PVSA). This analysis is crucial as it confirms the absence of sperm, typically conducted several weeks post-procedure to ensure complete clearance of sperm beyond the obstruction point. Despite its high success rate, the procedure is not without potential risks. Complications, although rare, can include infection, sperm granulomas (inflammatory reactions to sperm leakage), and chronic scrotal pain, each occurring in approximately 1% of cases. Moreover, about 0.24% of men may require a repeat vasectomy due to incomplete obstruction of the vas deferens initially [52].

Advantages and Limitations

The advantages of vasectomy include its one-time procedure nature, cost-effectiveness compared to female sterilization methods such as tubal ligation, and its non-reliance on daily compliance, unlike hormonal contraceptives. From a broader perspective, vasectomy offers a nearly immediate return to normal activities, with many men resuming work and other routine activities within a few days post-procedure, barring strenuous exercise or heavy lifting.

Nonetheless, one important factor to take into account is that although most vasectomies are reversible through a process called vasovasostomy, vasectomy reversals are sometimes more expensive and complex than the initial vasectomy treatment, and they are not always successful. Healthcare providers need to have important conversations with possible candidates about psychological preparedness and making the decision to never father children. Many studies showing no significant causal relationships have essentially disproved concerns regarding possible long-term impacts, such as an increased risk of prostate cancer [52].

The surgical intervention described above, which requires the cutting and sealing of the vas deferens, classifies vasectomy as an invasive procedure unlike other non-invasive contraceptive methods such as condoms or hormonal treatments. Although typically performed in an outpatient setting under local anesthesia, the nature of the operation introduces risks associated with surgical interventions, such as infection, bleeding, and in rare cases, chronic pain. Furthermore, the invasiveness of a vasectomy comes with a psychological burden due to its permanence and the significant consideration required before undergoing the procedure. These factors collectively explain the need for potential candidates to thoroughly weigh the invasiveness and possible irreversibility of a vasectomy against its benefits as a highly effective form of contraception. This level of invasiveness

and the associated post-operative care distinguish vasectomy from other less invasive male contraceptive options that do not require surgery and offer reversible effects.

In conclusion, vasectomy represents a safe, efficient, and cost-effective method of permanent male contraception that aligns well with the needs of many men seeking reliable long-term contraception. Its minimal impact on sexual function and overall health, combined with a high success rate, underpins its widespread utilization. However, the decision to undergo a vasectomy should be made with thorough understanding and consideration of its permanent nature and potential psychological impacts. This decision-making process benefits greatly from a comprehensive consultation with a healthcare provider, discussing all aspects of the procedure, expected outcomes, and possible future considerations.

Appendix E - Extended Discussion on Hormonal Male Contraceptive Methods

Hormonal male contraceptives

The concept of hormonal male contraception revolves around the manipulation of the male hormonal system to temporarily suppress spermatogenesis, thereby preventing pregnancy. This approach, developed substantially since its initial exploration in the 1970s, utilizes the administration of hormones such as testosterone, often in combination with a progestin, to significantly reduce the levels of gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones are essential for the production of sperm, and their suppression disrupts the normal sperm development process within the testes [61]. Historically, the use of exogenous testosterone to suppress spermatogenesis was first systematically studied by organizations such as the National Institute of Child Health and Human Development (NICHD) and the World Health Organization (WHO). These studies confirmed that hormonal male contraceptives could achieve contraceptive efficacy comparable to female methods, with minimal side effects, establishing a promising foundation for further development.

Comparative Analysis, Advantages, and Limitations

Contrary to physical barrier methods like condoms, or permanent solutions such as vasectomies, hormonal male contraceptives offer a reversible, systemic approach to preventing pregnancy. Unlike condoms, which provide immediate but use-dependent protection, or vasectomies, which are invasive and often irreversible, hormonal methods provide a sustained, reversible suppression of fertility through a non-invasive administration. The primary advantage of this method lies in its reversibility and the potential to share contraceptive responsibility more evenly between genders. However, the system's efficacy heavily depends on consistent adherence to the prescribed regimen, whether it involves regular injections, daily pills, or other forms of hormonal delivery. Despite the high efficacy under controlled conditions, real-world effectiveness can be compromised by non-compliance. Furthermore, the hormonal approach may induce side effects such as mood changes, weight gain, and other androgen-related effects, which need to be managed carefully. Long-term effects and complete reversibility are also critical areas requiring more extensive longitudinal studies to ensure these methods do not have lasting impacts on male fertility or overall health [61].

In the following sections, we will delve into the specific formulations of hormonal male contraceptives, focusing particularly on the innovative gel and oral forms that have been developed recently. While acknowledging the variety of other hormonal methods that have been explored, including injectables and implants, our attention will center on

these newer, less invasive options that promise ease of use and potentially broader appeal. These developments represent significant advancements in the field of male contraception, offering alternative solutions that cater to varying preferences and lifestyles.

Gel

The development of the transdermal Nestorone® (segesterone acetate) and testosterone (NES/T) gel represents a significant innovation in the field of hormonal male contraception. This gel combines segesterone acetate, a potent progestin, with testosterone, delivered in a transdermal system designed to suppress spermatogenesis effectively while maintaining secondary sexual characteristics and libido through hormonal balance. The chemical composition of the NES/T gel includes segesterone acetate, which uniquely binds to the progesterone receptor without cross-reacting with other steroid receptors such as androgens or estrogens, thus minimizing potential off-target hormonal effects [43]. Testosterone in the gel maintains the physiological functions typically regulated by endogenous testosterone, which are disrupted by the suppression of gonadotropins due to the progestin.

Mechanism of Action and Target Effects

The primary mechanism of action of the NES/T gel involves the suppression of the hypothalamic-pituitary-gonadal (HPG) axis. Segesterone acetate effectively suppresses the secretion of gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH)—from the pituitary gland [43]. This suppression decreases the intratesticular testosterone levels necessary for spermatogenesis. Orally, segesterone acetate has a low bioavailability and is not efficiently absorbed, which is why it is administered in the gel form [31]. Meanwhile, the exogenous testosterone in the gel compensates for the lower systemic levels of testosterone resulting from HPG axis suppression, thus supporting sexual function, muscle mass, and overall energy levels. The gel is applied to the skin, allowing for consistent absorption of the hormones, which helps to mitigate fluctuations in hormone levels that could affect efficacy and tolerability [43].

Contraceptive Efficacy

An interventional study conducted by Ilani et al. [22] explored the effectiveness of combining testosterone (T) gel with nestorone (NES) transdermal gels to suppress spermatogenesis, compared to using them separately. This study was pivotal in establishing the foundational basis for combining these two gels into a single formulation. It was designed as a randomized, double-blind, comparator clinical trial and carried out at two academic medical centers, focusing on assessing the efficacy of T gel alone and in combination with NES gel in reducing sperm concentration to 1 million/ml or less. To ensure the validity

and reliability of the findings, 99 healthy male volunteers were enrolled and randomly assigned to three distinct intervention groups: Group 1 received T gel 10 g with NES 0 mg/placebo gel; Group 2 received T gel 10 g with NES gel 8 mg; and Group 3 received T gel 10 g with NES gel 12 mg. This randomization was crucial to minimize selection bias and confounding variables. The treatment protocol involved daily application of the transdermal gels over a period of 20-24 weeks, with consistent monitoring of outcomes [22].

In this true experimental design, the independent variables were the concentrations of T and NES in the transdermal gels. The primary dependent variable was the sperm concentration in semen, with other dependent variables including serum concentrations of total and free testosterone, LH, and FSH. By controlling extraneous variables such as participants' health status, age range, and treatment adherence, the study aimed to isolate the effect of the intervention on spermatogenesis suppression. The primary outcome variable was defined as the percentage of men achieving a sperm concentration of 1 million/ml or less, serving as a quantifiable measure of contraceptive efficacy [22].

Efficacy analysis included 56 subjects who adhered strictly to the study protocol. The results demonstrated a significant difference in achieving the primary outcome among the groups. In Groups 2 and 3 (T + NES 8 mg and T + NES 12 mg), 89% and 88% of participants, respectively, reached the target sperm concentration, a remarkable outcome compared to only 23% in the placebo group (T + NES 0 mg) [22]. This suggests that the combination of T and NES effectively suppressed spermatogenesis, validating the hypothesis that these hormonal combinations can be a reliable male contraceptive method. Importantly, serum testosterone levels were maintained within the normal range for adult males, and reported adverse effects were minimal across all groups, indicating the safety of this intervention. This controlled experimental approach, with careful consideration of both primary and secondary outcomes, highlighted the potential of T and NES gels as a viable male contraceptive method [22].

Building on this foundation, an ongoing Phase IIb clinical trial, as detailed by Louwagie et al. [31] and Amory et al. [1], is expanding the scope by investigating the efficacy of a self-administered transdermal gel containing testosterone and segesterone acetate (NES/T). This international multicenter study employs a more extensive interventional design, involving 462 couples across 17 medical centers in 8 U.S. states and 7 other countries. Participants are using one of two T doses (either 8 mg/62 mg or 8 mg/74 mg) compounded with NES/T. The study employs a multi-phase structure, starting with screening and treatment initiation, followed by a 52-week efficacy phase, which requires sperm suppression to $\leq$1 million sperm/mL within 20 weeks. A subsequent recovery phase monitors sperm production post-treatment and assesses symptoms in both male and female partners [31, 1].

This interventional study is noteworthy for its detailed design, incorporating multiple

layers of outcome measurement. The primary endpoint is the rate of pregnancy during the efficacy phase, a direct indicator of contraceptive success. Secondary endpoints include the proportion of males achieving sufficient sperm suppression, side effects, hormone concentrations in participants and their partners, sexual function, and regimen acceptability. By structuring the study into these phases and using comprehensive measures, researchers aim to control for variables such as participant adherence and hormonal fluctuations, enhancing the study's validity and potential generalizability. Additionally, the daily gel application method offers a less invasive alternative to injectable contraceptives, addressing the need for more user-friendly contraceptive options [31].

The anticipated completion of the primary endpoint, contraceptive efficacy, is projected for late 2024, with full results expected in early 2025 [31]. These trials, through rigorous experimental design and careful consideration of both primary and secondary outcomes, represent a significant advancement in male contraception. They offer a promising alternative to existing methods and hold the potential to reduce unintended pregnancies upon successful completion and approval of the NES/T gel formulation [1]. This research underscores the importance of interventional studies in advancing contraceptive science by providing robust evidence for the efficacy and safety of new contraceptive methods.

Advantages and Limitations

One of the primary advantages of the NES/T gel is its non-invasive, reversible nature, offering an alternative to more permanent or invasive methods like vasectomy. Additionally, the gel's mode of application aligns with daily routines, potentially increasing user compliance and acceptance. The use of a transdermal delivery system minimizes the risk of gastrointestinal side effects often associated with oral hormonal agents and bypasses the liver, reducing metabolic burdens often seen with oral steroids.

However, the daily application requirement may also pose a limitation in terms of lifestyle adaptability and long-term adherence. Some users may find daily skin application cumbersome or may have concerns about transference to partners or others through skin contact, although studies have shown that proper application minimizes this risk. Furthermore, discontinuation rates in clinical trials have highlighted issues such as minor skin irritation and the discipline required for daily use, which could impact widespread acceptability and consistent use [43].

In summary, while the transdermal NES/T gel offers a promising approach to male contraception with a favorable safety profile and good efficacy, its success in broader populations will depend on addressing potential barriers to adherence and acceptance. Ongoing studies and eventual market introduction will further elucidate the role of this novel contraceptive technology in family planning and its potential to shift the paradigm in male responsibility for contraception.

Oral

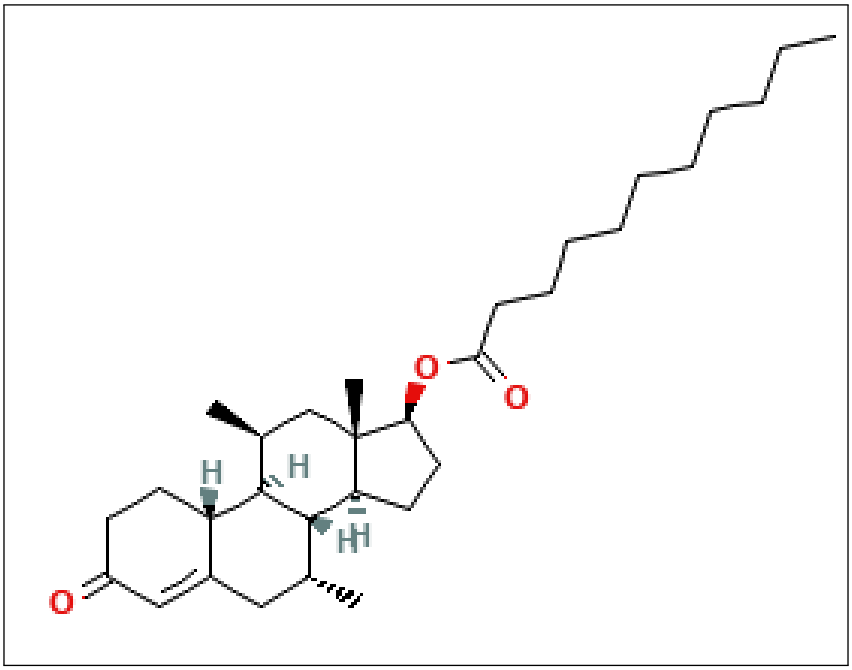

Figure ϕ_A**:** *Chemical structure of dimethandrolone undecanoate (DMAU), a synthetic testosterone derivative. The undecanoate ester at the C17 position enhances lipid solubility and prolongs metabolic stability. The steroid backbone selectively binds to androgen and progesterone receptors, suppressing gonadotropin secretion by modulating hypothalamic-pituitary signaling. Resistance to aromatization, due to the stable A-ring configuration, prevents estrogenic side effects, making DMAU a promising candidate for hormonal male contraception.*

Dimethandrolone undecanoate (DMAU) and 11β-methyl-19-nortestosterone dodecylcarbonate (11β-MNTDC) also represent promising developments in hormonal male contraception, besides NES/T. According to Louwagie et al. [31], DMAU is a pro-drug of dimethandrolone (DMA), a synthetic steroid derived from testosterone. Unlike testosterone, DMAU is structurally altered by the addition of an undecanoate ester at the 17-beta position, which enhances its oral bioavailability and pharmacokinetic profile. Dimethandrolone undecanoate (DMAU) is a synthetic testosterone derivative designed to suppress gonadotropin secretion through its selective binding to androgen (AR) and progesterone (PR) receptors. Figure ϕ_A depicts the molecular structure of DMAU, highlighting its mechanism of action. The undecanoate ester at C17 extends lipid solubility, enabling slow hydrolysis and sustained bioavailability. The steroid nucleus binds selectively to AR and PR, modulating electron density at receptor interaction sites through delocalized π-electrons in the conjugated steroid system. This binding disrupts luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion by inhibiting gonadotropin-releasing hormone (GnRH) signaling in the hypothalamus-pituitary axis, suppressing spermatogenesis. Additionally, DMAU resists aromatization due to its stable A-ring configuration, preventing electron rearrangement necessary for conversion to estrogen. This structural resistance avoids estrogenic side effects like gynecomastia, mak-

ing DMAU a safer alternative in hormonal male contraception. DMAU and DMA are characterized by their high affinity for androgen receptors (AR) and a lesser degree for progesterone receptors (PR), which plays a crucial role in their mechanism of action for male contraception [31]. Critically, DMAU and DMA are not aromatized into estrogenic compounds, thus they do not exert any estrogenic effects, which distinguishes them from other androgens that can contribute to side effects through estrogen pathways [31]. The mechanism by which DMAU suppresses spermatogenesis involves the inhibition of gonadotropin secretion from the pituitary gland. By binding to AR and PR, DMAU suppresses the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are essential for the initiation and maintenance of spermatogenesis in the testes. This suppression leads to a significant decrease in intratesticular testosterone, effectively reducing sperm production to levels consistent with contraceptive efficacy.

DMAU's efficacy and safety have been under investigation in various clinical settings, centered on understanding its pharmacokinetic (PK) properties and pharmacodynamic (PD) effects. In 2014, a key study explored oral dosing of DMAU in powder form ranging from 25 to 800 mg. This study utilized a crossover design, administering doses either in a fasting state or after a high-fat meal to evaluate the impact of dietary fat on drug absorption [3]. The study involved intensive sampling for PK analysis, with blood samples collected up to 24 hours post-dosing to determine DMAU's maximum concentration (Cmax), time to reach maximum concentration (Tmax), and area under the curve (AUC). Results showed a dose-dependent increase in DMAU absorption when taken with a high-fat meal. Significant suppression of gonadotropins was observed at doses of 200 mg and above, indicating effective biological activity at these levels [3].

A follow-up study in 2017 further investigated daily dosing of DMAU up to 400 mg, assessing its effects on hormone levels and overall tolerability [3]. Employing a double-blind, randomized, placebo-controlled design, participants received daily doses of DMAU and underwent monitoring for hormonal effects, including changes in testosterone and estrogen levels, and assessments of safety and tolerability. Blood samples were collected pre-dose and at intervals post-dosing on the first and last days of the study to evaluate the PK profile and hormonal changes. Improved DMAU absorption was noted with high-fat meals, and a dose-dependent suppression of testosterone and estrogen was observed without any serious adverse effects, supporting DMAU's potential for daily use as a male contraceptive [3].

In a phase I trial, a placebo-controlled, double-blinded, randomized study was conducted at two academic medical centers involving healthy men aged 18 to 50. Participants were grouped to receive 0, 100, 200, or 400 mg of DMAU orally, alongside meals containing 25–30 g of fat to emulate a Western diet. Extensive pharmacokinetic (PK) sampling was conducted on days 1 and 28, accompanied by regular monitoring of hormone levels—including luteinizing hormone (LH), follicle-stimulating hormone (FSH),

and testosterone—and spermatogenesis markers. Thirumalai et al. [58] found that even at the lowest dose of 100 mg, there was significant suppression of LH and FSH. Notably, the 400 mg dose effectively reduced sperm production to potentially contraceptive levels, with suppression of serum testosterone below castrate levels in many participants. Importantly, no serious side effects were reported, although some participants experienced reductions in libido or erectile function at the highest dose [58]. These outcomes suggest potential for DMAU in daily contraceptive regimens, particularly when considering its ability to maintain physiological androgenic effects and avoid significant liver toxicity.

Currently, trials at the University of California Los Angeles and the University of Washington are exploring the safety and pharmacodynamics of DMAU. These studies involve intramuscular and subcutaneous injections at doses ranging from 80 to 800 mg, as well as oral administration with or without levonorgestrel to suppress spermatogenesis over 12 weeks [7]. The research aims to optimize dosing strategies and evaluate long-term hormonal suppression and safety profiles, with completion expected by late 2024.

Turning to 11β-MNTDC, this testosterone derivative is also active at both AR and PR but is structurally designed to minimize estrogenic effects. Clinical evaluations indicate that 11β-MNTDC, when administered orally, effectively suppresses serum gonadotropins without significant liver toxicity. A key study by Drs. Wang and Page in 2020 employed daily dosing of 200 or 400 mg for 28 days, confirming that 11β-MNTDC is well-tolerated and capable of suppressing LH and FSH to levels likely to inhibit spermatogenesis effectively [31].

Both compounds, DMAU and 11β-MNTDC, have shown promise in early clinical evaluations for safety, tolerability, and effectiveness in suppressing spermatogenesis. However, significant research remains, particularly in phase II and III trials, to fully establish their profiles as viable daily male contraceptives. These studies will need to further address the long-term effects, optimal dosing regimens, and comprehensive safety profiles, including potential impacts on mood, libido, and metabolic parameters. As these trials progress, the potential for these novel agents to contribute significantly to the diversification of male contraceptive options becomes increasingly likely [31].

Overall, while hormonal male contraceptives present a significant advancement in shared contraceptive responsibility, they require careful consideration of their advantages against potential risks and side effects, emphasizing the need for ongoing research and development to optimize these therapies for wider acceptance and use.

References

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[65] Zhao, Y., Deng, S., Li, C., Cao, J., Wu, A., Chen, M., Ma, X., Wu, S., & Lian, Z. The role of retinoic acid in spermatogenesis and its application in male reproduction. *Cells*, 13(1092). 2024. https://doi.org/10.3390/cells13131092. This is a highly detailed resource on the role of retinoic acid in spermatogenesis. I make use of this paper broadly in Chapter two of Section two in my paper to back up claims I make about retinoic acid and its role in spermatogenesis.

[66] Zhong, X., Li, N., Liang, S., Huang, Q., Coukos, G., & Zhang, L. Identification of microRNAs regulating reprogramming factor LIN28 in embryonic stem cells and cancer cells. *The Journal of Biological Chemistry*, 285(53), 41961–41971. 2010. https://doi.org/10.1074/jbc.M110.169607. I make use of this paper in explaining the effect of inhibiting Lin28 on spermatogonia differentiation.